Genosensor Consortium (c/o Houston Advanced Research Center)

Development of the Electronic DNA Chip

By the early 1990's, biological researchers were beginning to make great strides in DNA analysis and apply their findings to important areas, including human diagnostics, agriculture, and toxicology. However, these efforts proceeded slowly due to a lack of efficient, cost-effective sequencing tools. In response, a multidisciplinary group of organizations came together in 1992 and formed a consortium to develop an advanced form of DNA sequence analysis that would be simpler, faster, and less expensive than currently used methods. The new technology, in the form of a tabletop scientific instrument, would be capable of rapidly analyzing nucleic acid sequences contained in a DNA molecule analyzed on a microarray (a matrix containing many gene sequences that could be evaluated simultaneously) on a microfabricated chip. The consortium believed that this new technology, called genosensor technology, would revolutionize DNA sequence analysis and result in multibillion-dollar annual U.S. sales.

To obtain the resources needed to undertake the project, the Genosensor Consortium sought financial assistance. Private firms were unwilling to fund a project that could not prove a guaranteed return on investment, so the group submitted a proposal to the Advanced Technology Program (ATP) and was awarded cost-shared funding for a five-year project. By the end of the project in 1998, the Genosensor Consortium had produced two laboratory prototypes, using DNA microarrays, that demonstrated significantly higher throughput for DNA sequence analysis and lower costs than was available through current methods. Three consortium members have commercialized the new technology. The market is still emerging and they anticipate a profit in the future. The ATP-funded project resulted in numerous patents, publications, and presentations.

COMPOSITE PERFORMANCE SCORE
(based on a four star rating)
* * *

Research and data for Status Report 92-01-0044 were collected during September – December 2003.

New Tools for DNA Analysis Are Needed

By 1992, DNA analysis was viewed as the key to understanding complex diseases, drug effects and toxicology, mutations, and pathogens. However, traditional methods for sequencing DNA were slow, costly, and labor-intensive. Gel electrophoresis, for example, involved separating nucleic acids or proteins on the basis of size, electrical charge, and other physical properties. Although accurate, it was time-consuming and tedious. The DNA had to be prepared prior to sequencing and the fragments could take a long time to detect. Furthermore, only a few fragments could be analyzed at one time.

By the early 1990s, several new techniques had been developed that were faster and more efficient. One technique involved using fluorescent tags on DNA fragments so that hybridized sequences could be identified in real time. This method, which was also automated, resulted in increased throughput (for example, 400 base pairs of DNA could be sequenced in a day, with a throughput of approximately 10,000 nucleotides). However, the time required for the entire DNA sequencing process did not decrease because DNA samples still had to be prepared.

Genosensor Consortium to Develop Advanced DNA Sequence Analysis Technology

In 1992, a multidisciplinary group of organizations came together and formed a consortium to develop a faster, more economical technology for DNA sequencing. The new technology, called genosensor technology, would

be in the form of a small scientific instrument consisting of a microfabricated chip containing DNA probes (an array), as well as associated sensor and computer technology. It would be able to instantaneously analyze the sequence of nucleic acids in a DNA molecule.

In the early 1990's, the use of DNA arrays was a promising solution for decreasing the time, effort, and expense in DNA analysis. With a DNA array, which includes a large number and high density of probes and the use of fluorescent dye labeling to detect base-pairing or hybridization, many gene expressions can be observed simultaneously. This was significant because, although every cell contains the same genetic material, the pattern of genes that are expressed in that cell characterizes its state of health or disease.

The Genosensor Consortium included Baylor College of Medicine; Beckman Instruments, Inc.; Genosys Biotechnologies, Inc.; Houston Advanced Research Center (HARC); Laboratories for Genetic Services, Inc. (LGS); Lincoln Laboratory, Massachusetts Institute of Technology (LL/MIT); MicroFab Technologies, Inc. Triplex Pharmaceutical Corporation. Genometrix, Inc. later joined the group.

Genosensor Consortium Anticipates Broad-Based Benefits

The Genosensor Consortium believed that the new technology would provide important benefits in areas such as human diagnostics, agriculture, and toxicology.

In the early 1990's, the use of DNA arrays was a promising solution for decreasing the time, effort, and expense in DNA analysis.

In human diagnostics, the genosensor could be used to quickly detect mutations within genes associated with diseases, such as cystic fibrosis, Alzheimer's, and cancer. Treatment could then be provided to a patient early enough to prevent the onset of a serious medical condition. The information could also be used to rapidly screen individuals who carry recessive genetic diseases and to provide them with genetic counseling when appropriate.

In agriculture, information obtained from genome sequencing could be used to rapidly develop new techniques for genetic engineering in crops and livestock, resulting in strains more resistant to disease and harsh climates and crops with a greater yield or higher nutritional value.

In toxicology, genosensors could be used to quickly detect genetic mutations in an individual that are caused by chronic exposure to radiation or chemical agents in the environment. With this knowledge, affected individuals could obtain treatment earlier, and employers could take steps to reduce chemical or radioactive hazards in the workplace, thereby decreasing work-related healthcare costs and disability claims.

New Technology Poses High Risk

The combination of small physical scale and efficiency of microelectronics and data processing in the consortium's proposed genosensor would increase the throughput of DNA sequencing by a hundredfold. This would result in a significant reduction in the cost of sequencing. However, developing the genosensor technology would also involve a high level of risk. It was a new technology in which the following six physical sciences and biotechnologies, rarely paired in the past, would be brought together in new ways:

- Chemistry of oligonucleotide synthesis
- Chemistry and biophysics of DNA hybridization
- Microluminescence and microelectronic detection
- Microlithography of solid supports
- Micro-robotics and microfluidics
- Parallel computer processing

Due to the risks, as well as the resources required for this multidisciplinary project, the consortium sought financial support. Private firms were unwilling to fund a project that could not prove an immediate return on investment, so the Genosensor Consortium submitted a proposal to ATP. In 1992, it was awarded $9.2 million in cost-shared funding.

Genosensor Technology Is Successfully Developed

The Genosensor Consortium organized the ATP project into five tasks:

- *Genosensor Development.* This would involve creating two types of DNA chips: a permittivity DNA chip and an optical or fluorescence DNA chip. (Permittivity is the measure of the ability of a material to resist the formation of an electric field within it.) In a permittivity DNA chip, hybridization is detected through electrical permittivity changes that occur at the array surface upon binding with DNA targets. In an optical or fluorescence DNA chip, hybridization is detected through an optical or fluorescent change that occurs at the array surface upon binding with DNA targets.
- *Instrumentation Development*. This would involve constructing the necessary electronic interface to connect the permittivity and optical genosensors with the computer workstation required for DNA sequence recognition.
- *Computer Development*. This would involve creating the software and hardware needed to associate the two-dimensional hybridization pattern on the genosensor array to the correct analysis of the sequence of nitrogenous bases that make up the target DNA molecule.
- *System Integration*. The group would assemble the deliverables from the genosensor, instrumentation, and computer technology development programs into demonstrable laboratory prototypes for DNA sequence analysis.
- *Applications Development*. The group would use the prototype systems to diagnose Lesch Nyhan and cystic fibrosis diseases.

HARC would play a central role in the development of the technology. It would fabricate different types of arrays using technology and techniques that had been established at LL/MIT. It would then conduct hybridization analyses with Baylor to determine the best substrate material to use for both the permittivity and optical DNA chips, while Triplex developed the DNA probes. HARC would then conduct sensitivity studies for the instrumentation to quantitatively determine the required signal amplification and noise rejection levels; and, with LL/MIT, would take measurements from both hybridized and non-hybridized DNA attached on the DNA chip prototypes to determine the specification requirements for the instrumentation boards. With Beckman Instruments and Baylor, HARC would develop fluorescent dye chemistry that could be used as an optical marker for detecting a hybridization event on the array.

Researchers believed that microarray technology for DNA analysis could be used for preventative medicine.

Much of the computer development also would take place at HARC: algorithms would be developed on a computer workstation at the research center; PC boards to host special purpose chip processors to increase computational speed would be assembled; and, optimal array studies would be performed.

Finally, the system prototypes would be integrated at HARC with guidance from Beckman Instruments. The mutation detection applications would be developed at HARC and at LGS.

By the end of the ATP-funded project, the consortium had accomplished the following:

- Invented several new electrical and optical methods for detecting hybridization on DNA microarrays, based on the application of microelectronics principles.
- Achieved highly resolved (50-mm) fluorescent images of DNA microarrays without the use of lenses. This enhanced by tenfold the sensitivity and the ability to scan large arrays of DNA probes very quickly (nine microarrays per second). This technology was unique and resulted in an issued patent.
- Developed permittivity-based detection. This approach may lead to the development of integrated DNA microarray devices that can directly detect hybridization through electrical permittivity changes that occur at the array surface upon binding DNA targets. This technology was also unique and was patented.
- Developed designs for an integrated DNA microarray device to electrically enhance the rate of DNA hybridization. These designs were patented.

- Developed a conceptual framework for achieving the desired sample throughput criteria required for pharmaceutical and diagnostic applications, whereby the solid support underlying the array would be carefully modified. This would result in a significant increase in the rate of target binding to the microarray, under low salt conditions. The consortium also developed various chemistry modifications. The modifications resulted in at least a tenfold improvement in the rate of hybridization.

In 1998, the consortium demonstrated two prototype systems. The first system, developed by Beckman Coulter, Inc. (Beckman Instruments had acquired Coulter Corporation in 1997), had fully automated hybridization and detection. The second system, developed by Genometrix, had at least a tenfold speed improvement over conventional microarray imagers. Both prototype systems represented advancements in the miniaturization of pharmaceutical and diagnostic platforms.

The ATP-Funded Project Benefits Participants

The ATP-funded project was beneficial to all of the consortium members. Genometrix, a provider of genomic services and information, was incorporated in 1993. In 1994, it received $300,000 for start-up costs from a venture capitalist. The company attributed its ability to attract this financing to the ATP award. From 1994 to 1998, Genometrix grew from 3 part-time to 40 full-time employees. That year, the company also had more than 20 partners, including LL/MIT and Motorola. The company believed that the ATP award played an important role in its growth.

Genosys Biotechnologies, a supplier of custom synthetic DNA and gene arrays, also benefited from the ATP-funded project. The company found that its participation proved valuable in helping it evaluate the most effective methods to produce and analyze gene arrays for new product and custom service development.

For Beckman Coulter, a leading provider of instrument systems and complementary products that simplify and automate laboratory processes, the ATP-funded project influenced its decision to further develop nucleic acid diagnostics technology.

Genosensor Technology Is Commercialized

Genometrix, Genosys Biotechnologies (now Sigma Genosys), and Beckman Coulter commercialized the genosensor technology.

Genometrix

Genometrix planned to market a wide range of products and services, which it would offer to genomic, pharmaceutical, and diagnostic customers. First, the company planned to offer genotype database services. Its database would use a panel of genetic markers to predict the effect of a drug, in terms of toxicity and efficacy, based on an individual's genetic profile. Pharmaceutical companies could then subscribe to the database and use it to screen patients for clinical trials, which would significantly increase the success rate of the trials and reduce the development time of a new drug.

Genometrix's next goal was to become a leading supplier of cost-effective, high-throughput, microarray-based products and genotype information services for the research and development of genomics-based pharmaceuticals. Finally, the company wanted to become a leading supplier of microarray-based diagnostic instrumentation. The instrumentation would be used to rapidly diagnose patient illness and to select optimum molecular medicines for treatment.

By March 2000, Genometrix was selling DNA chip microarrays for the high-throughput analysis of genetic variation, gene expression profiling, and other data analysis and storage services. The company was also constructing a DNA repository that it planned to license to customers, such as Schering-Plough and the National Cancer Institute, for use in genotyping analysis. In June, Michael Hogan, the chief scientific officer of Genometrix and a professor at Baylor College of Medicine, collaborated with two colleagues to test DNA microarray technology for screening DNA samples from patients with lung cancer to determine if their genes are different from those of healthy people. The group planned to eventually use these data to determine the probability that an individual would develop lung cancer.

DNA microarray technology was becoming successful by mid-2000. However, the technology was also creating its own problems. According to an article in the

June 2000 issue of the journal OncoLog, the speed and efficiency of the technology generated more data points than could be evaluated by conventional data analysis methods. To solve this problem, information specialists at Genometrix and the M.D. Anderson Cancer Center at the University of Texas began to develop new statistical techniques to handle the large volume of data.

By October 2000, Genometrix was providing sample analysis and database services for genotyping and gene expression applications to Schering-Plough Research Institute and similar organizations for research, discovery, and clinical trial applications. In January 2001, Genometrix collaborated with Vistagen, Inc. to combine in vitro stem cell biology with microarrays to discover surrogate markers for toxicology. The markers would be used in the development of pharmaceuticals.

In March 2001, the company released the VistaLogic Information System, an integrated, PC-based bioinformatics system for genomic researchers. Genometrix was also making plans to use its DNA chip microarrays for protein analysis and had partnered with Motorola to develop DNA clinical systems. The company also joined with GE Medical Systems to research the use of molecular imaging techniques with genetic probes to develop technologies for detecting and quantifying risk levels for diseases such as breast and prostate cancers.

Three years after the ATP-funded project ended, Genometrix had not only met, but had exceeded most of its original goals for commercialization. However, in spite of its technical successes, the company was also experiencing financial difficulties. In 2001, a year after announcing that it would make an $84 million initial public offering, it withdrew the filing due to concerns about market conditions and the general decline in the biotechnology industry. In 2002, Genometrix sold its intellectual property rights to the array technology and its tangible assets to High Throughput Genomics Inc. a genomics firm in Tucson, Arizona. Shortly thereafter, the company filed for bankruptcy and went out of business.

Genosys Biotechnologies (now Sigma Genosys)

In 1998, Genosys Biotechnologies was acquired by Sigma Aldrich and its name changed to Sigma Genosys. After the ATP-funded project, Sigma Genosys collaborated with HARC to evaluate custom oligonucleotide-based arrays (an oligonucleotide is a linear sequence of up to 20 nucleotides, the basic building blocks of nucleic acids) for gene expression profiling (the analysis of gene expression patterns). In 1999, the company introduced Panorama Gene Arrays for gene expression profiling. In 2003, Sigma Genosys also sold human cancer oligoarrays. These arrays represent 2,886 genes and have demonstrated greater specificity, sensitivity, and accuracy than similar oligo tests.

In 2003, the company was one of the largest suppliers of custom oligos for a variety of uses, including DNA primers (segments of DNA that are complementary to a given DNA sequence), antisense therapeutics (a means of treating many diseases that are difficult to control, such as cancer and viral infections, by blocking the messenger RNA transcripts used to produce disease-causing proteins), and DNA probes.

Beckman Coulter

At the end of the ATP-funded project in 1998, Beckman Coulter was very optimistic about genosensor technology and its potential for growth. The company anticipated that it would apply genosensors and related nucleic acid technologies to clinical diagnostics. It also envisioned that, in the future, nucleic acid diagnostics would not only replace current diagnostic methods, but could lead to the development of far more advanced diagnostic methods.

That year, Beckman Coulter signed several collaborative agreements to share intellectual property with Affymetrix, a biomedical company that develops state-of-the-art technology for acquiring, analyzing, and managing complex genetic information for use in biomedical research. In 2002, Beckman Coulter was granted an option to license technology for analyzing single nucleotide polymorphisms (SNPs), markers of genetic diversity, from Orchid BioSciences, Inc. a company with expertise in SNPs and a leader in genetic diversity. This technology, SNP-IT, which was developed in another ATP-funded project, is used to search for specific SNPs on strands of DNA to discover potential interaction sites for drugs. In 2003, Beckman Coulter was also leveraging Orchid's work on an image analyzer. According to Jim Osborne, Vice President of Advanced Technology at Beckman Coulter, the

company gained expertise in the ATP project that led to its relationship with Orchid.

In July 2003, Beckman Coulter formed a limited liability corporation with Affymetrix to further array commercialization efforts, such as the Miniature Integrated Nucleic Acid Diagnostic (MIND) device developed by Affymetrix in another ATP-funded project. The MIND device can rapidly and accurately diagnose a wide variety of diseases by extracting DNA from a small sample of blood and analyzing it through DNA probe-array hybridization.

In 2003, Beckman Coulter has also started to commercialize arrays. The company has continued to work with consortium members LL/MIT and Baylor and is seeking additional alliances.

Conclusion

With ATP's assistance, the Genosensor Consortium accomplished its goal. It successfully developed an advanced form of DNA sequence analysis, an electronic chip, using novel microarrays. The new chip can analyze DNA faster, more efficiently, and at less cost than previous methods.

Since 1997, three of the consortium members have commercialized the technology. Genometrix was the first member to sell microarray-based products and services; by 2000, these included microarrays for high-throughput analysis of genetic variation and for gene expression profiling, data analysis, sample analysis, and database and storage services. That year, however, due to the economic downturn, which had a significant effect on the biotechnology industry, the company was acquired by High Throughput Genomics.

Sigma Genosys (formerly Genosys Biotechnologies) has also commercialized the new technology; by 2003, its products included Panorama Gene Arrays for gene expression profiling and human cancer oligoarrays. In 2003, Beckman Coulter also began to commercialize arrays.

The market for microarray-based products and services has continued to expand. As of 2004, there were many companies in the biomedical, pharmaceutical, and agriculture industries that had commercialized arrays.

During the ATP-funded project, members of the Genosensor Consortium received one patent, published numerous papers, and gave a number of presentations on their research.

PROJECT HIGHLIGHTS
Genosensor Consortium (c/o Houston Advanced Research Center)

Project Title: Development of the Electronic DNA Chip (Genosensor Technology Development)

Project: To develop a microfabricated chip that incorporates synthetic DNA probes, together with necessary sensor and computer technology, for an automated, low-cost DNA sequencer.

Duration: 8/18/1993-7/31/1998
ATP Number: 92-01-0044

Funding (in thousands):

ATP Final Cost	$9,234	50%
Participant Final Cost	$9,366	50%
Total	$18,600	

Accomplishments: ATP funding enabled the Genosensor Consortium to develop an electronic chip for DNA sequence analysis using miniaturization, microelectronics, and data processing. The new chip was simpler to use, more efficient, and less expensive than other current means of performing DNA sequence analysis.

By the end of the ATP-funded project, the consortium had accomplished the following:

- Invented several new electrical and optical methods for detecting hybridization on DNA microarrays, based on the application of microelectronics principles.
- Achieved highly resolved (50-mm) fluorescent images of DNA microarrays without the use of lenses. This enhanced by tenfold the sensitivity and the ability to scan large arrays of DNA probes very quickly (nine microarrays per second).
- Developed permittivity-based detection. This approach may lead to the development of integrated DNA microarray devices that can directly detect hybridization through electrical permittivity changes that occur at the array surface upon binding DNA targets.
- Developed a conceptual framework for achieving the desired sample throughput criteria required for pharmaceutical and diagnostic applications, whereby the solid support underlying the array would be carefully modified. This would result in a significant increase in the rate of target binding to the microarray, under low salt conditions. The consortium also developed various chemistry modifications. The modifications resulted in at least a tenfold improvement in the rate of hybridization.
- Developed designs for an integrated DNA microarray device to electrically enhance the rate of DNA hybridization.

The Genosensor Consortium members filed and were granted the following patent:

- "Multi-site detection apparatus " (No. 5,532,128: filed December 12, 1994; granted July 2, 1996)

Commercialization Status: Three of the consortium members have commercialized products resulting from their project research. For example, Genometrix began to sell microarray-based products and services in 1997, during the ATP project. The company earned revenue of $2 million for these products and services that year. By 2000, the company specialized in DNA chip microarrays for genetic variation and gene expression profiling and offered services for data analysis and storage. It also provided sample analysis and database services for genotyping and gene expression research; its customers included organizations such as the Schering Plough Research Institute. In 1999, Sigma Genosys began to sell Panorama Gene Arrays, which profile gene expression in human cytokines, B. subtilis, and E. coli. In 2003, the company sold human cancer oligoarrays. In 2003, Beckman Coulter started to commercialize arrays.

Outlook: Since 1997, the market for microarray-based products and services has continued to grow. In 2003, there were a number of companies that had commercialized arrays for differential expression. These companies have not made a substantial profit yet, but they anticipate an increasing demand for their products in the future.

Composite Performance Score: ***

Consortium Members:

- Houston Advanced Research Center (HARC)
- Baylor College of Medicine
- Genometrix, Inc.
- Lincoln Laboratory, Massachusetts Institute of Technology (LL/MIT)
- Sigma Genosys (formerly Genosys Biotechnologies, Inc.)
- Beckman Coulter (formerly Beckman Instruments, Inc.)
- Dynacare/Dynagene (formerly Laboratories for Genetic Services, Inc.)
- MicroFab Technologies, Inc.
- Antigenics (formerly Triplex Pharmaceutical Corporation)

PROJECT HIGHLIGHTS
Genosensor Consortium (c/o Houston Advanced Research Center)

Company:
Beckman Coulter, Inc.
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P.O. Box 8000
Brea, CA 92822-8000
(Beckman Coulter is one of the companies commercializing the technology)

Contact: Jim Osborne
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The group also shared its project research in many publications and presentations.

Publications:

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Presentations:

- Eggers, M.E., W.J. Balch, L.G. Mendoza, R. Gangadharan, A.K. Mallik, M.G. McMahon, M.E. Hogan, D. Xaio, T.R. Powdrill, Bonnie Iverson, G.E. Fox, R.C. Willson, K.I. Maillard, J.L. Siefert, and N. Singh. "Advanced Approach to Simultaneous Monitoring of Multiple Bacteria in Space," 27th International Conference on Environmental Systems, Lake Tahoe, NV, July 14-17, 1997.
- Matson, R.S. "Recent Developments in Ras Oncogene Screening," Biochip Array Analysis 3rd Annual Conference, International Business Communications, San Diego, CA, March 5-6, 1997.
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PROJECT HIGHLIGHTS
Genosensor Consortium (c/o Houston Advanced Research Center)

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